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CHEMOTHERAPY: A new standard combination for recurrent ovarian cancer?

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Abstract

Ovarian cancer that recurs more than 6 months following primary chemotherapy can respond to many different drugs, but retreatment with a combination of carboplatin and paclitaxel has become a standard of care. A combination of pegylated liposomal doxorubicin and carboplatin may provide a slightly but significantly greater therapeutic index than carboplatin and paclitaxel.

Despite improvements in cytoreductive surgery and primary chemotherapy, the majority of women with epithelial ovarian cancer experience recurrence of their disease. If clinically apparent ovarian cancer persists and grows during primary therapy with carboplatin and paclitaxel, the cancer is considered platinum-refractory. For patients who experience a complete clinical remission with no anomalies visible on imaging and normal CA125 levels in the blood, recurrence within 6 months of completing primary chemotherapy indicates platinum-resistant ovarian cancer. The longer the interval between the completion of chemotherapy and disease recurrence, the more likely the cancer is to be platinum sensitive; with objective response rates to retreatment with platinum-based regimens of 50% or more when progression-free survival (PFS) after primary therapy exceeds 2 years.

In addition to platinum compounds and taxanes, a variety of agents have demonstrated activity in platinum-sensitive recurrent ovarian cancer including pegylated liposomal doxorubicin (PLD), topotecan, gemcitabine, vinorelbine, pemetrexed, and etoposide. Traditionally, platinum-sensitive recurrent ovarian cancer has first been treated with carboplatin alone or in combination with paclitaxel. One recent study, however, suggests that another combination may confer a marginally better outcome.

The ICON4/AGO-OVAR 2.2 trial demonstrated that a combination of carboplatin and paclitaxel provided superior PFS by a median of 3 months ($P = 0.0004$) and overall survival by 5 months ($P = 0.02$) when compared to treatment with carboplatin alone for patients with platinum-sensitive disease (Table 1).¹ Similarly, a combination of gemcitabine and carboplatin provided a median of 2.8 months improvement in PFS ($P = 0.0031$) when compared with carboplatin alone, but no improvement in overall survival.² Combinations that improve the outcome produced by carboplatin and paclitaxel in recurrent ovarian cancer have not been previously identified.

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In a new study published in the *Journal of Clinical Oncology*, Pujade-Lauraine and colleagues reported that a combination of PLD and carboplatin provided significantly improved PFS compared to the now standard therapy of paclitaxel and carboplatin.³

Platinum-sensitive patients with a 6-month-free interval after primary or secondary treatment with platinum and taxane were randomly assigned to receive either carboplatin (area under the curve 5) and PLD (30 mg/m²) every 4 weeks or carboplatin (area under the curve 5) and paclitaxel (175 mg/m²) every 3 weeks. After a median follow-up of 22 months, PFS was significantly greater with PLD and carboplatin than with paclitaxel and carboplatin (11.3 months versus 9.4 months, $P < 0.005$). Although improvement in median PFS was less than 2 months, there was also a difference in the toxic effects profile that favored the PLD and carboplatin combination. Severe nonhematologic toxic effects were more frequent in the paclitaxel and carboplatin arm (36.8% versus 28.4%, $P < 0.01$). More frequent grade 2 or greater alopecia (83.6% versus 7%), hypersensitivity reactions (18.8% versus 5.6%) and sensory neuropathy (26.9% versus 4.9%) were observed in the paclitaxel and carboplatin arm, whereas more hand-foot syndrome (12% versus 2.2%), nausea (35.2% versus 24.2%) and mucositis (13.9% versus 7%) were observed in the PLD and carboplatin arm.

Hypersensitivity reactions were temporally attributed to administration of carboplatin rather than paclitaxel and occurred despite the use of prophylactic steroids administered before paclitaxel treatment. A decreased incidence of hypersensitivity reactions to carboplatin was also seen by the Southwest Oncology Group in patients receiving the combination of PLD and carboplatin in comparison to patients receiving carboplatin alone.⁴ None of the 31 patients treated with PLD and carboplatin developed a hypersensitivity reaction, whereas 9 of 30 (30%) patients treated with carboplatin alone developed acute hypersensitivity ($P = 0.0008$) with five reactions being greater than grade 2 in severity.⁴

In the literature, allergic reactions to cisplatin and carboplatin have been observed in 10–27% of treated patients, particularly after repeated administration of the drug.⁵ Mechanisms underlying hypersensitivity to platinum compounds remain uncertain, but characteristic clinical features are consistent with a type I IgE mediated reaction that would require interaction of T cells and B cells.⁵ Doxorubicin is lymphocytotoxic and is one component of regimens used to treat both T-cell and B-cell lymphomas. Early studies documented the capacity of doxorubicin to suppress the production of IgG and IgM antibodies,⁶ although inhibition or stimulation of the humoral response as a result of exogenous antigens depended critically on the interval between the administration of doxorubicin and challenge with antigen.⁷ To date, the immunosuppressive effect of PLD on production of IgE antibodies in preclinical models has not been analyzed.

PLD and carboplatin seems to improve PFS; however, data are not sufficiently mature to determine whether the combination improves overall survival when compared with paclitaxel and carboplatin. Both drugs are widely approved and reimbursed for the care of ovarian cancer patients. Consequently, there should be no barriers to the use of this combination for the management of platinum-sensitive recurrent ovarian cancer, particularly in patients with neuropathy from primary treatment who do not have compromised cardiac function.

When combinations of novel and conventional agents improve PFS, but overall survival is not yet available, access to the new agent can be delayed, as improved overall survival has often been required for regulatory approval and reimbursement. In another report, Monk, *et al.*⁸ found that a combination of trabectedin (1.1 mg/m²) and PLD (30 mg/m²) every 3 weeks improved PFS compared with PLD (50 mg/m²) alone every 4 weeks. Again, the improvement in PFS was modest but statistically significant (1.5 months overall and 1.7 months in platinum-sensitive patients, $P = 0.019$ and $P = 0.017$, respectively). Neutropenia and hepatic dysfunction

were more frequent with trabectedin plus PLD whereas hand-foot syndrome and mucositis was more frequent with PLD alone. Overall survival data for platinum-sensitive patients are not yet available. On the basis of this trial, trabectedin has been approved by the European Medicines Agency but has not been recommended for approval by the Oncologic Drugs Advisory Committee of the FDA.⁹

In trials of first-line therapy, an excellent correlation has been observed between PFS and overall survival. This result led a panel convened in the USA by the FDA, ASCO and American Association for Cancer Research to recommend that PFS be a surrogate for overall survival in trials of primary therapy.¹⁰ For trials of recurrent disease, the correlation of PFS and overall survival is less certain and the panel felt that additional data were needed before a definitive recommendation regarding use of PFS as a surrogate for overall survival is considered. After completing treatment on randomized studies, patients can often cross over to the study drug or receive different regimens of other active agents. Thus, proponents of PFS as an endpoint feel that overall survival analysis can be confounded by subsequent therapy. Opponents argue that the impact of drugs should be sufficiently robust to result in improved overall survival regardless of subsequent therapy. In contrast to trials of primary therapy, there have been few large randomized trials for recurrent disease. When the current trials mature, we will have additional data points to better judge the value of PFS as a surrogate for overall survival in platinum-sensitive ovarian cancer.

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Biography

Robert C. Bast Jr earned his M.D. at Harvard Medical School, Boston, USA and completed his training in internal medicine and medical oncology at Johns Hopkins Hospital, Baltimore, USA, Peter Bent Brigham Hospital, Boston, USA and the Dana-Farber Cancer Institute, Boston, USA. He completed predoctoral and postdoctoral fellowships at Massachusetts General Hospital, Boston, USA and the National Cancer Institute, Bethesda, USA. He is currently Vice President for Translational Research at the University of Texas M. D. Anderson Cancer Center, Houston, USA and holds the Harry Carothers Wiess Distinguished University Chair in Cancer Research. His research interests include biomarkers, imprinted tumour suppressor genes, aberrant signaling, autophagy, tumour dormancy, targeted therapy in ovarian and breast cancer, and genes which regulate paclitaxel sensitivity

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Table 1

Combination chemotherapy for platinum-sensitive recurrent ovarian cancer.

Drug regimens	Number of patients	Progression-free survival (months)	Overall survival (months)
Paclitaxel and carboplatin versus carboplatin ¹	802	13 versus 10 ($P = 0.0004$)	29 versus 24 ($P = 0.02$)
Gemcitabine and carboplatin versus carboplatin ²	356	8.6 versus 5.8 ($P = 0.0031$)	18 versus 17.3 ($P = 0.7349$)
PLD and carboplatin versus carboplatin ⁴	61	12 versus 8 ($P = 0.02$)	31 versus 18 ($P = 0.2$)
PLD and carboplatin versus paclitaxel and carboplatin ³	976	11.3 versus 9.4 ($P = 0.005$)	Too early (NA)
Trabectedin and PDL versus PDL ⁷	672	9.2 [*] versus 7.5 ($P = 0.017$)	Too early (NA)

* Platinum-sensitive patients only. Abbreviations: NA, not available; PDL, pegylated liposomal doxorubicin.